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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,754	07/06/2001	Keith D. Allen	R-372	4570

26619 7590 07/16/2004

DELTAGEN, INC.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,754	ALLEN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16 and 23-33* is/are pending in the application.

4a) Of the above claim(s) *16 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 May 2004 has been entered.

Claims 16 and 23 were previously withdrawn from consideration and claims 24-33 were considered in the Office Action mailed 24 December 2002. Claims 28-32 were amended in the 10 May Paper. Claims 16 and 23-33 are pending and claims 24-33 are under consideration.

Response to Amendment

Claim Rejections - 35 USC § 112

Rejection of claims 29-31 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps is withdrawn.

New Grounds

Claim Objections

Claims 24, 27-31 and 33 are objected to because of the following informalities: The claims are objected to for using an undefined abbreviation. Each abbreviation used in the claims should be defined when it is first used. Amending claim 24 to recite the full name of the mTMT gene would overcome this objection. Appropriate correction is required.

Claim Rejections - 35 USC § 101/§112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 24-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial credible asserted utility or a well-established utility.

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. §112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001

The Examiner is using the following definitions in evaluating the claims for utility.

"Specific"-A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial"-A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible"- Credibility is assessed for the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established"-a specific, substantial and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material alone or taken with the knowledge of one skilled in the art.

The application claims a transgenic mouse comprising a homozygous disruption in an endogenous mTMT gene, wherein the transgenic mouse exhibits a phenotype selected from decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio and increased pre-pulse inhibition, all relative to wild-type mice. Further claims are directed to a

cell or tissue isolated from the transgenic mouse, a method of producing the transgenic mouse, a targeting construct that can be used to produce the mouse, a method of making the targeting construct and a mouse embryonic stem cell transformed with the targeting construct.

Although the claims were not previously rejected as lacking utility, upon further consideration, it is clear that the disclosure fails to teach a specific and substantial utility for the claimed invention. All of the teachings in the specification regarding how one might use a transgenic animal comprising the recited genotype and phenotype are based on the assertion that the animal and cells isolated therefrom are models for disease. For example, on page 18, first full paragraph, the specification teaches, "[t]he cell- and animal-based systems described herein can be utilized as models for diseases" and "the animal- and cell-based models may be used to identify drugs, pharmaceuticals, therapies and interventions that may be effective in treating disease." In the second full paragraph on page 18, the specification teaches, "cells are examined to determine whether one or more of the disease cellular phenotypes has been altered to resemble a more normal or more wild type, non-disease phenotype." On page 19, lines 28-30, the specification teaches, "[t]he transgenic animals and cells of the present invention may be utilized as models for diseases, disorders, or conditions associated with phenotypes relating to a disruption in a tryptase."

With regard to the utility of the claimed mouse and cells as a disease model, it is first noted that the phenotypic differences identified in mice comprising a homozygous disruption of an endogenous mTMT gene relative to wild-type mice are very small and do not appear to be statistically significant (see especially Figures 3-5). Given that phenotype of the claimed mouse is statistically the same as that of a wild-type mouse, it logically would not be possible to

establish a statistically significant amelioration of those differences. Thus, additional experimentation is required to reasonably establish that the phenotypic differences asserted in the application are of sufficient magnitude to be useful as a model.

Furthermore, even if the phenotype of the claimed mouse were significantly different from a wild-type mouse, neither the specification nor the art provides a specific and substantial teaching of what disease state is modeled by the animal. All of the teachings in the specification regarding the utility of the claimed animal as a disease model are general in nature and would apply to any transgenic animal exhibiting an altered phenotype. Although the specification discloses that the mouse exhibits decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio and increased pre-pulse inhibition, all relative to wild-type mice, there is no teaching what specific disease state is being modeled. The specification asserts that the transgenic animals and cells may be utilized as models for diseases, disorders, or conditions associated with phenotypes relating to a disruption in a tryptase, but provides no specific teaching as to what diseases, disorders, or conditions relate to a disruption in a tryptase. As established in the Office Action mailed 10 May 2002, the phenotype arising from disruption of any given gene in any given animal is highly unpredictable (see especially the discussion beginning in the first full paragraph on page 7). Therefore, it cannot be asserted the phenotypic characteristics disclosed for the claimed mouse are relevant to any other species of mammal comprising a disruption in an endogenous mTMT gene without additional experimentation to reasonably confirm that this is the case. Thus, the utility asserted for the claimed animal is neither specific, because the specification fails to identify the specific disease state modeled by the animal, nor substantial, because it is merely an invitation to the skilled artisan to experiment

and identify which, if any, diseases are modeled by the claimed invention. Thus, neither the specification nor the art provide a specific and substantial use for claimed mouse.

With regard to cells isolated from the claimed mouse, the specification clearly fails to establish said cells as a model because there is no disclosed difference between cells established from the claimed mouse and wild type cells other than the recited disruption in an endogenous mTMT gene. However, the specification fails to teach a specific and substantial use for a cell that merely comprises a disruption in an endogenous mTMT gene.

The claims directed to reagents to be used in making the claimed mouse, and methods of making the reagents and mouse, lack utility because the mouse made thereby is not supported by a specific and substantial utility. Likewise, claim 33, which is directed to a method of identifying an agent that modulates a phenotype associated with disruption in an mTMT gene, lacks utility because, for the reasons discussed above, the skilled artisan would not know what to do with an agent that modulates the phenotypes disclosed for a mouse comprising a homozygous disruption in an endogenous mTMT gene. A method of assaying for, identifying or making a material that itself has no specific and/or substantial utility lacks a substantial "real world" utility.

For these reasons, the disclosure fails to adequately support the claimed subject matter with a teaching of a specific and substantial use for the claimed invention and therefore fails to meet the requirements of 35 U.S.C. §101. To overcome this rejection, Applicant should explicitly identify an assertion within the specification of a specific and substantial credible utility for the claimed invention and establish a probative relation between any evidence of record and the originally disclosed properties of the claimed invention.

Claims 24-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-33 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are directed to a transgenic mouse comprising a homozygous disruption in an endogenous mTMT gene, wherein the transgenic mouse exhibits a phenotype selected from decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio

and increased pre-pulse inhibition, all relative to wild-type mice, to a cell or tissue isolated from the transgenic mouse, to a method of producing the transgenic mouse and a method of using the transgenic mouse. In the first full paragraph on page 7, the specification defines "disruption" as encompassing both inhibition and enhancement of the normal gene products activity. Thus, the claims encompass a transgenic mouse comprising any disruption resulting in inhibition or enhancement of an endogenous mTMT gene activity, which exhibits the phenotypes recited in the claims, as well as reagents used to make the mouse, cells established from the mouse, methods of making the mouse and a method of using the mouse. As the claimed invention is based, in part, on a mouse comprising a disruption leading to enhancement of an endogenous mTMT gene activity and exhibiting a defined phenotype, it is incumbent upon the disclosure to describe the genotypic and phenotypic characteristics of such a mouse.

Although the specification does not explicitly disclose the type of disruption comprised by the mouse reduced to practice in the working examples, it is most likely, given the structure of the targeting construct used (see especially Example 1 and Figures 2A –2B), that the disruption resulted in complete inhibition of functional mTMT expression. Thus, the phenotypes disclosed are those resulting from complete inhibition of mTMT function. The specification provides no teachings with regard to the phenotype associated with disruptions leading to enhancement of endogenous mTMT gene activity. However, based on sound scientific reasoning, the skilled artisan would reasonably conclude that a mouse comprising only enhanced mTMT function relative to a wild type mouse would not have the same phenotype as a mouse lacking mTMT function. Thus, the specification fails to teach either the phenotypic characteristics of a mouse comprising enhancement of mTMT function or the additional

genotypic modifications required to produce a mouse comprising enhancement of mTMT function and the phenotypic characteristics recited in the claims.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of transgenic mice, reagents and methods of the claims. Therefore, only the described mouse comprising homozygous disruption resulting in complete inhibition of mTMT gene function and the phenotypes established in the working examples, as well as a cell or tissue isolated from the transgenic mouse, a method of producing the transgenic mouse and a method of using the transgenic mouse comprising homozygous disruption resulting in complete inhibition of mTMT gene function and the phenotypes established in the working examples meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 24-33 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples;

(f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a transgenic mouse comprising a homozygous disruption in an endogenous mTMT gene, wherein the transgenic mouse exhibits a phenotype selected from decreased body weight, decreased thymus weight, decreased thymus weight to body weight ratio and increased pre-pulse inhibition, all relative to wild-type mice, to a cell or tissue isolated from the transgenic mouse, to a method of producing the transgenic mouse and a method of using the transgenic mouse. In the first full paragraph on page 7, the specification defines "disruption" as encompassing both inhibition and enhancement of the normal gene products activity. Thus, the enabling specification must teach the skilled artisan how to make a mouse comprising a disruption resulting in both inhibition and enhancement of an endogenous mTMT gene activity, which exhibits the phenotypes recited in the claims.

Amount of direction provided by the inventor and existence of working examples: Although the specification does not explicitly disclose the type of disruption comprised by the mouse reduced to practice in the working examples, it is most likely, given the structure of the targeting construct used (see especially Example 1 and Figures 2A –2B), that the disruption resulted in complete inhibition of functional mTMT expression. Thus, the phenotypes disclosed are those resulting from complete inhibition of mTMT function. The specification provides no teachings with regard to the phenotype associated with disruptions leading to enhancement of endogenous mTMT gene activity.

State of the prior art and level of predictability in the art: The art teaches that the phenotype arising from any given genotypic modification is unpredictable. For example, Doetschman (1999) *Lab. Animal Sci.* 49:137-143 teaches, "[o]ne often hears the comment that genetically engineered mice…are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype. These expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies" (page 137, paragraph 1). Doetchman goes on to teach, "it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies" (page 140, column 2, third full paragraph) and "[a]pparent lack of phenotype more likely reflects or inability to ask the right questions, or our lack of tools to answer them" page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation of a transgenic mouse is highly unpredictable and in some cases requires empirical experimentation to uncover. Thus, one of ordinary skill in the art would not reasonably expect that a mouse comprising all of the disruptions of an mTMT gene encompassed by the mouse of the claims would exhibit the recited phenotypes.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, one of ordinary skill would not be able to make the full scope of the animals claimed without undue experimentation. Given the art recognized unpredictability of phenotype arising from any given genotypic modification and the lack of teachings in the specification with regard to how to make a transgenic mouse comprising enhancement of endogenous mTMT gene activity and the phenotypic characteristics

recited in the claims, the skilled artisan would not know how to make the full scope of the claimed subject matter without undue experimentation. For this reason, only a mouse comprising a homozygous disruption resulting in complete inhibition of the normal gene products activity and exhibiting the phenotypes recited in the claims meets the "how to make" requirement of 35 U.S.C. §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is indefinite insofar as it depends from claim 27 and recites, "wherein said mouse comprises a homozygous disruption in an mTMT gene." There is no antecedent basis for a mouse comprising a homozygous disruption in claim 27, which is limited to a mouse comprising a heterozygous disruption.

Claim 29 is indefinite in reciting in step (b), "the pseudopregnant mouse gives birth". Once a blastocyst has been implanted in a pseudopregnant mouse the mouse is no longer pseudopregnant. The mouse is actually pregnant. Amending step (b) to read "...wherein the mouse gives birth..." would be remedial.

Claim 29 is further rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claim recites producing a transgenic mouse comprising introducing a murine

stem cell into a pseudopregnant mouse. It is understood in the art that a stem cell will not develop into a transgenic mouse unless said stem cell is first introduced into a blastocyst.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

Anne-Marie Falk

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